Methotrexate and Trimethoprim-Sulfamethoxazole for *Pneumocystis pneumonia* Prophylaxis

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To the Editor:

We read with interest the recent article by Katchamart, et al1 about Canadian recommendations for the use of methotrexate (MTX) in patients with rheumatoid arthritis (RA). The authors conclude that trimethoprim-sulfamethoxazole (TMP-SMX) should be avoided in RA patients treated with MTX. This recommendation was based on several case reports and a retrospective case-control study in which concomitant use of TMP-SMX and MTX was associated with blood dyscrasias1. In their cases, therapeutic doses of TMP-SMX were prescribed to treat urinary tract infection or other infections diseases, but chemoprophylactic doses of TMP-SMX for Pneumocystis pneumonia (PCP) were not included. We believe that these 2 clinical indications for treatment with TMP-SMX should be considered separately. In fact, the contraindication for TMP-SMX use for PCP prophylaxis has been described as “outdated” in a recent review article.

PCP caused by P. jirovecii, one of the serious opportunistic infections in immunocompromised hosts, has been reported in RA patients receiving low-dose MTX or combination therapy with MTX and tumor necrosis factor (TNF) inhibitors3. We previously reported the clinical characteristics of Japanese patients with RA who developed PCP during treatment with infliximab (IFX) and MTX4. Risk factors identified for PCP in RA patients receiving this treatment were age ≥ 65 years, a daily dose of at least 6 mg prednisolone, and coexisting pulmonary disease5. A metaanalysis suggested high efficacy for chemoprophylaxis with TMP-SMX against PCP in non-HIV-infected patients; the protection rate is almost 100% with adequate adherence and tolerance6. Because the incidence of PCP in RA patients receiving IFX and MTX in Japan is approximately 10- to 20-fold greater than that in Western countries, we recommended PCP chemoprophylaxis with TMP-SMX for those Japanese RA patients receiving IFX and MTX with the 3 risk factors described above4. The Japanese guidelines for the use of TNF inhibitors in RA patients were therefore amended, following our recommendation7.

Both MTX8 and TMP9 inhibit dihydrofolate reductase (DHFR), and SMX inhibits dihydrofolate synthesis10. It has been reported that TMP, as well as SMX, inhibited erythroid and granulocyte-monocyte colony formation in vitro, in a dose-dependent manner, and that this inhibition was reversed by folic acid10. These data suggest that higher dosages of TMP-SMX administered with MTX lead to a stronger inhibition of folate metabolism and induce blood dyscrasias. The dosage of TMP-SMX for chemoprophylaxis of PCP is only one-fourth to one-eighth that used for the prevention of PCP in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. Mayo Clin Proc 2007;82:1052-9.


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